J. Indian Chem. Soc.,
Vol. 76, November-December 1999, pp. 547-549

A convenient and efficient procedure for selective deprotection of acetates by titanium(IV) isopropoxide†

Brindaban C. Ranu*, Sankar K. Guchhait and Manika Saha

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Calcutta-700 032, India

Manuscript received 6 August 1999

A simple and efficient procedure for the deprotection of acetates using titanium(IV) isopropoxide has been demonstrated. A wide range of structurally varied acetates have been subjected to deprotection by this procedure to give the corresponding alcohols in high yields. This procedure offers remarkable selectivity for deprotection of acetate over benzoate, *p*-nitrobenzoate and allyl, benzyl, TBDMS and THP ethers.

Selective protection and deprotection of hydroxyl groups often require multistep organic synthesis[1]. Of the many methods available for hydroxyl group protection, acetates are among the preferred ones as they are very readily introduced and removed by a variety of reaction conditions[1]. The acetyl groups are normally removed by treatment with aqueous acid or base. But this reaction condition suffers from the disadvantages of not being compatible with several other hydroxyl-protecting groups such as benzoates, silyl ethers, THP ethers etc. However, selective deprotecting agents are particularly important and beneficial in complex synthetic sequences in which two protected hydroxyl groups must be unmasked at different stages of synthesis. Thus, efforts are continued to develop deprotection conditions to cleave acetates selectively in presence of other protecting groups. A number of reagents, such as Zn-MeOH[2], guanidine[3], *p*-toluenesulfonic acid adsorbed on silica gel[4], DBU in benzene[5], Mg-MeOH[6], magnesium methoxide[7], and bismuth(III) mandelate[8] among others have been reported for this purpose. But several of these reagents are associated with limitations with regard to general applicability, for example, Zn-MeOH, *p*-TsOH-SiO_2 and bismuth(III)-mandelate are effective only in the cleavage of aryl acetates, while $Mg(OMe)_2$ can not deprotect tertiary acetate. Moreover, Mg-MeOH is not compatible with many reducible functional groups like double and triple bond, carbonyl group, aromatic halides etc. Though these difficulties have been overcome using $Mg(OMe)_2$, it fails to provide selective deprotection of acetate over *p*-nitrobenzoate. Thus, the need of developing new and more effective deprotective reagent with general applicability and high selectivity in presence of other protecting groups is felt strongly.

During a course of another investigation we have observed a significant effect of titanium(IV) alkoxide towards deblocking of acetate to the corresponding alcohol. This prompted us to undertake a systematic investigation for the deprotection of acetate with a particular reference to its selectivity over other hydroxyl-protecting groups. Although titanium(IV) alkoxides are well known for effecting transesterification[9], to the best of our knowledge we are not aware of any study using it for selective deprotection of acetates.

$$ROAc \xrightarrow[THF,\ rt]{Ti(O^iPr)_4} ROH$$

Results and Discussion

In a typical experimental procedure, a solution of the acetate in THF was stirred with titanium(IV) isopropoxide at room temperature under nitrogen. After the reaction was over (TLC), the reaction mixture was quenched with HCl and usual work-up furnished the product. Other solvents such as methanol, ethanol and acetonitrile were also tried; however, the reactions in these solvents are not very clean, being associated with side-products. THF has been found to overcome such difficulties. Titanium(IV) ethoxide is also suitable for this reaction, but $Ti(O^iPr)_4$ is chosen for being less expensive.

A wide range of structurally varied acetates were subjected to deprotection by this procedure to produce the corresponding alcohols in good yields (Table 1). This reagent is equally effective for primary, secondary and tertiary acetates (entries 1–7). The phenolic acetates are also cleaved without any difficulty (entries 8–10). The reaction condition is quite compatible with chloro (entry 12), olefinic double bond (entry 11), nitro (entry 13), cyano (entry 25), epoxide (entry 26), α,β-unsaturated carbonyl (entry 29), aromatic aldehyde[10] (entry 10), *O*-benzylidene (entry 28) and carboxylic ester (entry 14) groups. A good selectivity is

†Dedicated to Professor D Nasipuri on the occasion of his 75th birth anniversary

Table 1. Deprotection of acetates with $Ti(OPr)_4$*

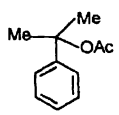
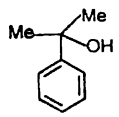
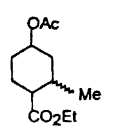
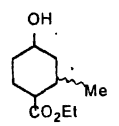
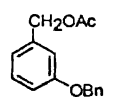
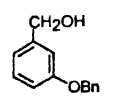
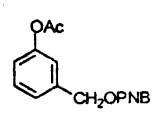
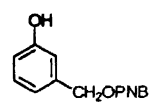
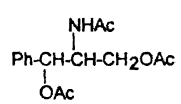
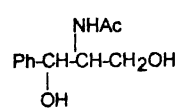
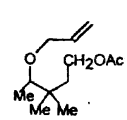
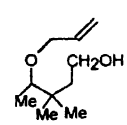
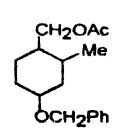
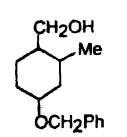
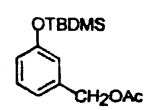
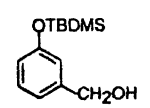
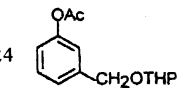
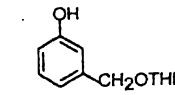
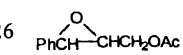
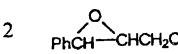
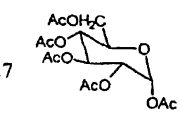
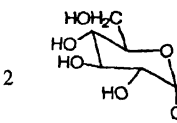
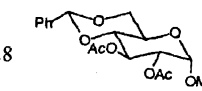
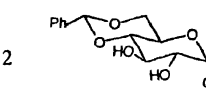
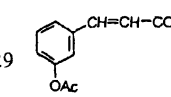
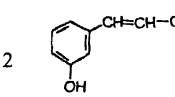
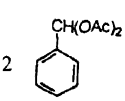
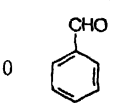
Entry	Acetate	Time(h)	Product	Yield(%)
1	$PhCH_2OAc$	14	$PhCH_2OH$	83
2	$Ph(CH_2)_2OAc$	10	$Ph(CH_2)_2OH$	85
3	$Ph(CH_2)_3OAc$	12	$Ph(CH_2)_3OH$	84
4	PhCH(Me)OAc	14	PhCH(Me)OH	85
5	Cyclohexyl acetate	12	Cyclohexanol	81
6	(–)-Menthyl acetate	11	(–)-Menthol	80
7		12		80
8	Phenyl acetate	10	Phenol	88
9	2-Naphthyl acetate	10	2-Naphthol	90
10	*m*-Acetoxybenzaldehyde	11	*m*-Hydroxybenzaldehyde	87
11	$PhCH{=}CHCH_2OAc$	12	$PhCH{=}CHCH_2OH$	86
12	*p*-Chlorobenzyl acetate	13	*p*-Chlorobenzyl alcohol	90
13	*m*-Nitrobenzyl acetate	12	*m*-Nitrobenzyl alcohol	76
14		14		75
15		12		76
16		10		75
17	PhNHCOMe	15	No reaction	
18		11		75
19	*p*-Methoxybenzyl acetate	12	*p*-Methoxybenzyl alcohol	86
20	*p*-Allyloxybenzyl acetate	14	*p*-Allyloxybenzyl alcohol	80
21		14		85
22		14		75
23		12		75

Table-1 (contd.)

24		6		76
25		12		90
26		12		85
27		12		80
28		12		75
29		12		90
30	$PhCH_2OCOCH_2Cl$	11	$PhCH_2OH$	90
31	$PhCH_2OCOCH_2OMe$	18	$PhCH_2OH$	88
32		10		90
33	$PhCH{=}CH{-}CH(OAc)_2$	10	$PhCH{=}CH{-}CHO$	92

*Yields refer to pure isolated products, properly characterised by spectral data; Bn = benzoyl, PNB = *p*-nitrobenzoyl.

found in the deprotection of acetate over benzoate (entry 15) and *p*-nitrobenzoate (entry 16). Acetamides are inert to this reagent (entry 17) and thus acetate functionality is demasked quite efficiently in presence of acetamide group (entry 18). This procedure also provides very high selectivity in the cleavage of acetates without affecting several important hydroxyl-protecting ether moieties such as methoxy (entry 19), allyloxy (entries 20, 21), benzyloxy (entry 22), ter-butyldimethylsilyloxy (entry 23) and tetrahydropyranyloxy (entry 24). The reaction condition is mild enough for deprotection of a chiral acetate without any racemization (entry 6). Chloro- and methoxyacetates are also deprotected by this reagent (entries 30, 31) and their rates of reaction are in this order : chloroacetate > acetate > methoxyacetate. This reagent has also been used for the deprotection of diacetates to aldehydes (entries 32, 33) which is also of considerable synthetic potential[11].

The reactions are, in general, very clean and high yielding. No side-product was isolated in any run. A stoichiometric amount of titanium tetraisopropoxide has been used,

and it was established that this amount is necessary for the reaction to go to completion[12].

To conclude, this titanium(IV)-mediated procedure provides a very simple and efficient methodology for selective deprotection of acetates. The notable advantages offered by this procedure are : (a) general applicability (effective for all types of acetates), (b) operational simplicity, (c) mild reaction conditions (room temperature, presence of no strong acid or base) compatible with OMe, CO_2Me, CN, Cl, NO_2, etc., (d) involvement of no toxic reagent and no environmental pollution from waste, (e) high yields of products (75–90%) and (f) remarkable selectivity (selective deprotection over benzoate, *p*-nitrobenzoate and allyl, benzyl, TBDMS, THP ethers). This method is a better and practical alternative to the existing procedures and we believe, it will find useful application particularly when selective deprotection of acetate is required in complex molecules containing more than one hydroxy-protecting moieties.

Experimental

The acetates were obtained commercially or prepared from the corresponding alcohols by standard procedures. Titanium (IV) isopropoxide (97%, Aldrich) was used as such. Tetrahydrofuran was distilled over potassium benzophenone immediately before use. Thin layer chromatography was done on precoated silica gel plates (E. Merck). Silica gel (60–120 mesh, SRL) was used for column chromatography. Petroleum ether refers to the fraction boiling in the range 60–80°.

General procedure for deprotection of acetates. Representative procedure : A solution of benzyl acetate (150 mg, 1 mmol) in THF (3 ml) was stirred with titanium(IV) isopropoxide (285 mg, 1 mmol) at room temperature (28°) under nitrogen for 10 h (monitored by TLC). The reaction mixture was then decomposed with a few drops of 4*N* HCl, being placed in an ice-water bath. THF was then stripped off under reduced pressure and the residue was extracted with ether (4 × 10 ml). The ether extract was washed with saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). Evaporation of the solvent furnished the crude product which was purified through a short column of silica gel, being eluted with petroleum ether-diethyl ether (9 : 1), to afford pure benzyl alcohol (90 mg, 83%) which was identical with an authentic sample (IR, ^1H NMR).

This procedure was followed for deprotection of all the acetates (Table 1). The products being known compounds were easily identified by comparison with the authentic samples[13]. Although the results reported (Table 1) were based on mmol-scale reactions, gram-scale reactions also afforded the corresponding products in analogously good yields.

Acknowledgement

The authors are pleased to acknowledge the financial support from C.S.I.R., New Delhi. Two of the authors (S.K.G. and M.S.) are also thankful to C.S.I.R. for their Fellowships. The authors sincerely thank Mr. Kallol Basu of I.I.T., Kanpur, for his help in the initial phase of this investigation during his two-month stay in this laboratory as a summer project student.

References

1. (a) T. W. Green and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Wiley, New York, 1991; (b) P. J. Kocienski, "Protective Groups", Thieme, Stuttgart, 1994.
2. A. G. Gonzalez, Z. D. Jorge and H. L. Dorta, *Tetrahedron Lett.*, 1981, **22**, 335.
3. N. Kunesch and C. M. J. Poisson, *Tetrahedron Lett.*, 1987, **28**, 3569.
4. G. Blay, M. L. Cardona, M. B. Garcia and J. R. Pedro, *Synthesis*, 1989, 438.
5. L. H. B. Baptistella, J. F. dos Santas, K. C. Ballabio and A. J. Marasaioli, *Synthesis*, 1989, 436.
6. Y. C. Xu, E. Lebeau and C. Walker, *Tetrahedron Lett.*, 1994, **35**, 6207.
7. Y. C. Xu, Bizuneh and C. Walker, *Tetrahedron Lett.*, 1997, **37**, 455; *J. Org. Chem.*, 1996, **61**, 9086.
8. V. Le Boisselier, M. Postel and E. Dunach, *Tetrahedron Lett.*, 1997, **38**, 2981.
9. (a) D. Seebach, E. Hungerbuehler, R. Naef, P. Schnurrenberger, B. Weidmann and M. Zueger, *Synthesis*, 1982, 138; (b) D. Ramon, G. Guillena and D. Seebach, *Helv. Chim. Acta*, 1986, **79**, 875; (c) M. Froneman and T. A. Modro, *Synthesis*, 1991, 201; (d) W. Oppolzer and P. Lienard, *Helv. Chim. Acta*, 1992, **75**, 2572; (e) D. Seebach, G. Jaeschke, K. Gottwald, K. Matsuda, R. Formisano, D. A. Chaplin, M. Breuning and G. Bringmann, *Tetrahedron*, 1997, **53**, 7539; (f) G. Shapiro and M. Marzi, *J. Org. Chem.*, 1997, **62**, 7096.
10. Aliphatic aldehydes, however, did not survive the reaction condition.
11. T. -S. Li, Z. -H. Zhang and C.-G. Fu, *Tetrahedron Lett.*, 1997, **38**, 3285.
12. Use of 0.5 equivalent of $Ti(O^iPr)_4$ in the deprotection of cyclohexyl acetate leads to only 50% completion of the reaction.
13. C. J. Pouchert, "The Aldrich Library of NMR Spectra", 2nd. ed., Aldrich Chemical Co., Inc., Milwaukee, 1983; Vols. 1 and 2.